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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SHIBUYA, MARK LANCE	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 03/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/927,161	DIAZ-TORRES ET AL.	
	Examiner	Art Unit	
	Mark L. Shibuya	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-7 and 10-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-7 and 10-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

1. Claims 1, 4-7 and 10-12 are pending. Claims 2, 3, 8, 9, and 13-19 are canceled. Claims 1, 4-7 and 10-12 are examined.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/16/2005 has been entered.

Election/Restrictions

3. The restriction and election of species requirement set forth in the Office action mailed 7/1/2003, and applicant's election of Group I and the species of Bacillus, entered 8/22/2003, are maintained.

Withdrawn Rejections

4. The rejection of claims 1, 4-7 and 9-12 under 35 U.S.C. 112, second paragraph, as indefinite, is withdrawn, in view of applicant's amendments to the claims, filed 12/16/2005.

5. The rejection of claims 1, 4-7 and 9-12 under 35 U.S.C. 112, first paragraph for new matter, is withdrawn, in view of applicant's amendments to the claims, filed 12/16/2005.

6. The rejection of claims 1, 4-7 and 9-12 under 35 U.S.C. 112, first paragraph for failing to comply with the enablement requirement, is withdrawn, in view of applicant's amendments to the claims, filed 12/16/2005.

New Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

7. Claims 1, 4-7 and 10-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, (and its dependent claims), recites the term "*Bacillus sp*", which renders the claim vague and indefinite because "*sp*" should be spelled out and not abbreviated. Claim 1 recites the term "non-critical targets", which renders the claim indefinite, because the term "non-critical targets" is not defined by the claim, the specification does not provide a standard for ascertaining which targets are non-critical, so that one of skill in the art would not be reasonably apprised of the metes and bounds of the claimed invention.

Claim 12 recites the language "a target sequence", which renders the claim vague and indefinite. There is uncertain antecedent basis for this limitation in the claim. The relationship between the target sequence in the chromosome and the endogenous sequences complementary to the flanking non-homologous sequences is not defined. Claim 12 recites the language "increasing the amount of sequence homology between said target sequence and said DNA construct", which renders the claim vague and

indefinite, because it is unclear whether the target sequence or the DNA construct is increasing in homology. Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step appears to be one of: increasing the amount of sequence homology by changing the target sequence in the chromosome *or* by changing the DNA construct, *or* by changing both the target and the construct.

New Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

8. Claim 12 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The specification does not appear to teach the method of claim 1, *further* comprising increasing the amount of sequence homology between a target sequence in a chromosome and the DNA construct of claim 1, wherein the DNA construct is *integrated* into the chromosome of *Bacillus* (see step (iii) of claim 1).

Maintained Claim Rejections - 35 USC § 112, First Paragraph

9. Claims 1, 4-7, and 9-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description Rejection. This rejection maintains the grounds for rejection of claims 1, 4-7, and 9-12 and claims 1-12 as set forth in the previous Office actions, mailed 7/27/2004 and 10/20/2003, respectively.

The claims are drawn to a methods for producing a transformed microorganism via chromosomal integration of exogenous DNA. Although the specification discloses examples directed to certain methods of transformation of Bacillus subtilis (see specification, p. 19, line 16), the specification and claims do not provide a representative number of individual species of Bacillus to sufficiently describe the class of Bacillus, and its specific subclasses, genera, and species. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Because the disclosure fails to describe the common attribute, characteristics or sequences that identify all of the members of the genus or a substantial portion thereof, and because the genus is enormous and highly diverse, the disclosure of a few species of the genus of Bacillus is insufficient to teach the entire

genus. Consequently, one of skill in the art would not be reasonably apprised of a representative number of species to describe the entire genus.

Claim 12 is drawn to the use of increasing the homology between a target sequence and a DNA construct for use in a method of producing a transformed organism. However, the structures and method steps disclosed would not reasonably apprise one of skill in the art as to what the applicant had possession of at the time of filing.

DNA homology is defined as "the degree of similarity (relatedness) between base sequences in different DNA molecules (or in different parts of the same molecule); two nucleic acid molecules which are 100% homologous have identical sequences of nucleotides, " (dictionary of Microbiology and Molecular Biology", 2nd Ed., Singleton et al., John Wiley and Sons, printed 1995 (see applicant's Information Disclosure Statement, Paper No. 9)). Thus, DNA homology is defined in terms of the identity of base order between two (or more) sequences, rather tan the extent (length of) of sequences comprising base order of a given identity. For example, two 10 base pair long DNA molecules that have 8 base pairs in common might be considered to be 80%. Likewise, two 1,000,000 base pair long DNA molecules that have 800,000 base pairs in common would be 80% homologous.

The specification, while lacking an explicit description defining the term "homology" seems to define apparently related terms in different ways:

"Homologous sequence" . . . is a sequence that is found in the same genetic source or species. For example, the host cell strain may be deficient in a specific gene.

If that gene is found in other strains of the same species the gene would be considered a homologous sequence."

This definition is confusing because; (a) there is no mention of sequence identity /similarity; (b) the explicit definition (the first sentence) reads on ay sequence found in the same species, irrespective of the degree of sequence identity or length of sequence; and (c) the meaning of "same genetic source" is unclear, especially because it is cast in the alternative to the term "species". The example confuses the issue even more because the meaning of the term "deficient" is unclear. Does it mean "functionally deficient" (i.e., the gene at issue contains a non- or mis-sense mutation in the coding region, or an inactivating mutation in the promoter region, or perhaps a deletion mutation?) Doe it mean that the gene at issue is absent entirely (i.e., the organism lacks a gene that confers resistance to erythromycin, or perhaps a plasmid that confers a pathogenic phenotype, e.g., *B. cereus* versus *B. anthracis*)? In the case wherein the gene is at issue is absent entirely, what is the meaning of the term "that gene" as "a homologous sequence" since no sequence identity is possible to a gene that is absent. Furthermore, exemplification does not constitute explicit definition. Also, it is unclear as to whether a homologous sequence must be perfectly homologous and whether a single base can be homologous.

"Homology Box- ". . . may flank each side of the incoming sequence. The sequence of each homology box is homologous to a sequence in the Bacillus chromosome. These sequences direct where in the Bacillus chromosome the new

construct gets integrated and what part of the bacillus chromosome will be replaced by the incoming sequence".

This definition is confusing because it relies upon the definition of "homologous sequence" discussed above. Moreover, it is explicitly directed to modification of Bacillus chromosomes and is therefore not commensurate with the broad scope of the claims.

The specification does not disclose core sequences or structures that have the property of being "non-critical targets for said microorganism to initiate uptake of said DNA construct" (as in claim 1) such that the practitioner would be apprised that applicant was in possession of the claimed invention.

Response to Arguments

Applicant argues that the amendment to claim 12 so as to recite increasing the homology between the target sequence and the construct, fulfills the written description requirement. Applicant argues that the statement in the Advisory action stating that Figure 11 discloses two non-homologous flanking regions of 2 kb and 1.5 kb as evidence that the genus of non-homologous sequences has been adequately represented.

Applicant's arguments filed 12/16/2004, have been fully considered but they are not persuasive.

Applicants do not provide a single example that explicitly describes an increase in sequence identity between a target sequence and a DNA construct. Example 5 of the specification is directed to ". . . varying the size of the homology box", which does not necessarily alter the percent homology between the construct and the target

sequence. Applicant define "target sequence" as ". . . the sequence where it is desired for the incoming sequence to be inserted into the . . . genome. The target sequence may encode a functional wild-type gene or operand, a functional mutant gene or operand, or a non-functional gene or operand". Thus the "target sequence" is physically defined by the extent of the region of the chromosome that undergoes recombination. In view of the definition provided for "homology box" the "target sequence" is in turn defined by the composition of the DNA construct. The term does not appear to refer to the chromosome as a whole, nor a substantial segment thereof.

Even if it were argued that "target sequence" includes the chromosome as a whole or a substantial segment thereof, and therefore an increase in the size of a homology box would constitute an increase in percent sequence identity between a target sequence and a DNA construct, applicant's Example 4 would appear to be in conflict with claim 12. Example 4 describes an increase in transformation efficiency brought about by the addition of non-homologous sequences to the distal portions of a DNA construct. Said addition would only decrease the degree of sequence homology between a target sequence (irrespective of how applicant's definition of that term is construed) and a DNA construct.

It remains unclear as to what range in length that the non-homologous region must be. For example, does a 1 base pair non-homologous sequence function as a non-critical target to initiate uptake of the construct. Can a megabase sequence so function? The specification does not indicate that the applicant was in possession of

the genus of non-homologous sequences that function as non-critical targets to initiate uptake of the construct.

Reasserted Claim Rejections - 35 USC § 102

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

10. Claims 1, 6, 7, 11 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Niaudet et al., Journal of Bacteriology, July 1985, Vol. 163, No. 1, pp. 111-120 (cited on PTO-892, mailed 10/20/2003). This rejection maintains the reasons of record, as set forth in the Office action mailed 10/20/2003, and is further necessitated by applicant's amendments to the claims, entered 12/16/2004. The claims are interpreted in light of the above rejections under 35 USC 112, second paragraph.

The claims are drawn to methods of producing a transformed microorganism, comprising: i) providing a competent microorganism (i.e., capable of transformation), wherein said microorganism is a *Bacillus sp.*; (ii) producing a DNA construct *in vitro*, wherein said DNA construct comprises an incoming sequence of interest, flanked on each side by a homology box, wherein said homology boxes are flanked by non-homologous sequences which are non-critical targets for said microorganism to initiate uptake of said DNA construct; and (iii) directly transforming said microorganism with said DNA construct such that the DNA construct becomes integrated into the chromosome of said microorganism.

Niaudet et al., throughout the publication and abstract, and at p. 111, para 3, line 62-col. 4, line 16, col. 6, line 1-col. 9, line 22, teach methods of producing a transformed

Bacillus subtilis (col. 2, lines 27-57) by introducing a DNA construct *in vitro*, wherein said DNA construct comprises an incoming sequence of interest that is a DNA fragment of a pHV32 plasmid (p. 113, caption to Fig. 1; for example, as in instant claim 7) which has been engineered into a pHV453 plasmid, (col. 5, lines 17-col. 34; and as in instant claim 11), and flanked on each side by the lateral sequences of the homologous sequences thyB and X (Niaudet at p. 113, para 2, and Fig. 1), which read on the homology boxes of the instant claims, wherein said homology boxes are flanked by non-homologous sequences of pHV453 plasmid that are, absent evidence to the contrary, "non-critical" targets for said microorganism to initiate uptake of said DNA construct; and (iii) directly transforming said microorganism with said DNA construct (p. 113, para 3-4) such that the DNA construct becomes integrated into the chromosome of said *B. subtilis*, (pp. 112-113, bridging paragraph and Figures 4 and 5). Niaudet, at p. 117, para 3-6, p. 119, para 4, and Fig. 5, teaches increasing the amount of sequence homology between a target sequence and a DNA construct, wherein **M** is a heterologous DNA segment and **a**, **b**, **c**, **k**, **l**, and **m** are homologous sequences flanking **M** and wherein **ω** is added, resulting in an increase in the amount of sequence homology.

Because the methods taught by Niaudet disclose the steps of the instant claimed invention, and because Example 4 in the instant specification discloses that "[t]he non-homologous flanks were derived from the TOPO cloning vector and were of E. coli based plasmid origin; therefore, the sequences were not expected to have any significant homology to regions in the Bacillus chromosome", absent evidence to the

contrary, the non-homologous sequences supplied by the pHV453 plasmid, are "non-critical targets" that act to initiate uptake of the DNA construct, in the same way as the instant claimed invention.

Response to Arguments

Applicant argues that Niaudet et al., fails to disclose homologous regions (i.e., homology boxes) flanked by non-homologous regions, as recited in the amended claims.

Applicant's arguments filed 12/16/2004, have been fully considered but they are not persuasive. Niaudet et al., teach homology boxes ThyB and X are flanked by non-homologous sequences of pHV453 (Niaudet at p. 113, para 2, and Fig. 1).

11. Claims 1, 6, 7, and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by van Sinderen and Venema, Journal of Bacteriology, Sept 1994, Vol. 176, No. 18, pp. 5762-5770 (cited on PTO-892, mailed 10/20/2003; formerly referred to a "Venema"). This rejection maintains the reasons of record, as set forth in the Office action mailed 10/20/2003, and is further necessitated by applicant's amendments to the claims, entered 12/16/2004. The claims are interpreted in light of the above rejections under 35 USC 112, second paragraph.

The claims are drawn to methods of producing a transformed microorganism, comprising: i) providing a competent microorganism (i.e., capable of transformation), wherein said microorganism is a *Bacillus sp.*; (ii) producing a DNA construct *in vitro*, wherein said DNA construct comprises an incoming sequence of interest, flanked on

each side by a homology box, wherein said homology boxes are flanked by non-homologous sequences which are non-critical targets for said microorganism to initiate uptake of said DNA construct; and (iii) directly transforming said microorganism with said DNA construct such that the DNA construct becomes integrated into the chromosome of said microorganism.

van Sinderen and Venema, throughout the publication and abstract, teach methods of producing a transformed *Bacillus subtilis* (col. 2, lines 27-57) by introducing a DNA construct *in vitro*, wherein said DNA construct comprises an incoming sequence of interest that is a DNA fragment encoding a *spoVG-lacZ* fusion protein (p. 5764, caption to Fig. 1), wherein spoVG is homologous *Bacillus* DNA, (p. 5762, para 2), and lacZ is heterologous DNA, (p. 5763, para 4), that have been engineered into the pBTW312 plasmid, (col. 5, lines 17-col. 34; and as in instant claim 11), and flanked on each side by the lateral sequences of the homologous *B. subtilis amyE* sequences (van Sinderen and Venema at p. 5764, caption to Fig. 1), which read on the homology boxes of the instant claims, wherein said homology boxes are flanked by non-homologous sequences of the pBTW312 plasmid that are, absent evidence to the contrary, "non-critical" targets for said microorganism to initiate uptake of said DNA construct; and (iii) directly transforming said microorganism with said DNA construct (p. 5764, para 4) such that the DNA construct becomes integrated into the chromosome of said *B. subtilis*, (p. 5765, para 5-p. 5767, para 1.

Because the methods taught by van Sinderen and Venema disclose the steps of the instant claimed invention, and because Example 4 in the instant specification

discloses that "[t]he non-homologous flanks were derived from the TOPO cloning vector and were of E. coli based plasmid origin; therefore, the sequences were not expected to have any significant homology to regions in the Bacillus chromosome", absent evidence to the contrary, the non-homologous sequences supplied by the vector, are "non-critical targets" that act to initiate uptake of the DNA construct, in the same way as the instant claimed invention.

Response to Arguments

Applicant argues that van Sinderen and Venema, fails to disclose homologous regions (i.e., homology boxes) flanked by non-homologous regions, as recited in the amended claims.

Applicant's arguments filed 12/16/2004, have been fully considered but they are not persuasive. van Sinderen and Venema teach homology boxes from the *B. subtilis amyE* gene that are flanked by non-homologous sequences of the pBTW312 plasmid (p. 5764, caption to Fig. 1).

12. Claims 1, 6, 7, and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Fahnestock et al., US 4,828,994 (cited on PTO-892, mailed 10/20/2003). This rejection maintains the reasons of record, as set forth in the Office action mailed 10/20/2003, and is further necessitated by applicant's amendments to the claims, entered 12/16/2004. The claims are interpreted in light of the above rejections under 35 USC 112, second paragraph.

The claims are drawn to methods of producing a transformed microorganism, comprising: i) providing a competent microorganism, (i.e., capable of transformation), wherein said microorganism is a *Bacillus sp*; (ii) producing a DNA construct *in vitro*, wherein said DNA construct comprises an incoming sequence of interest, flanked on each side by a homology box, wherein said homology boxes are flanked by non-homologous sequences which are non-critical targets for said microorganism to initiate uptake of said DNA construct; and (iii) directly transforming said microorganism with said DNA construct such that the DNA construct becomes integrated into the chromosome of said microorganism.

Fahnestock et al., US 4,828,994, throughout the patent and abstract, and at col. 3, line 62-col. 4, line 16, col. 6, line 1-col. 9, line 22, teach methods of producing a transformed *Bacillus subtilis* (col. 2, lines 27-57) by introducing a DNA construct *in vitro*, wherein said DNA construct comprises an incoming sequence of interest that is a DNA fragment of a heterologous functional cat gene (col. 4, lines 4-13; for example, as in instant claim 7) inserted into a cloned homologous apr gene (col. 5, lines 1-61; for example, as in instant claim 6) that has been inserted into a shuttle vector, (as in instant claim 10), which is capable of transformation and replication in both *E. coli* and *B. subtilis*, (col. 5, lines 17-col. 34); said apr gene coding for the *B. subtilis* protease subtilisin (col. 3, lines 5-8, fig. 1), and flanked on each side by the lateral sequences of the homologous apr gene, said lateral apr sequences reading on homology boxes, wherein said homology boxes are flanked by non-homologous sequences from said vector that are, absent evidence to the contrary, "non-critical" targets for said

microorganism to initiate uptake of said DNA construct; and (iii) directly transforming said microorganism with said DNA construct such that the DNA construct becomes integrated into endogenous apr gene on the chromosome of said *B. subtilis*, (col. 7, lines 31-54) in order to inactivate said endogenous apr gene (col. 2, line 58-col. 3, line 2; col. 3, lines 47-53).

Because the methods taught by Fahnestock disclose the steps of the instant claimed invention, and because Example 4 in the instant specification discloses that "[t]he non-homologous flanks were derived from the TOPO cloning vector and were of E. coli based plasmid origin; therefore, the sequences were not expected to have any significant homology to regions in the Bacillus chromosome", absent evidence to the contrary, the non-homologous sequences supplied by the vector, are "non-critical targets" that act to initiate uptake of the DNA construct, in the same way as the instant claimed invention.

Response to Arguments

Applicant argues that Fahnestock et al., US 4,828,994, fails to disclose the elements recited in the amended claims.

Applicant's arguments filed 12/16/2004, have been fully considered but they are not persuasive. The patent of Fahnestock et al., US 4,828,994, teaches all elements with regard to claims 1, 6, 7, and 10, as set forth above in the instant rejection. Applicant's arguments with regard to the rejection of claim 11 are persuasive and the rejection of said claim 11, as anticipated over Fahnestock, is withdrawn.

13. Claims 1, 6, 11 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Cooper et al., EP 0761815 A2 (cited on PTO-892, mailed 10/20/2003). This rejection maintains the reasons of record, as set forth in the Office action mailed 10/20/2003, and is further necessitated by applicant's amendments to the claims, entered 12/16/2004. The claims are interpreted in light of the above rejections under 35 USC 112, second paragraph.

The claims are drawn to methods of producing a transformed microorganism, comprising: i) providing a competent microorganism, (i.e., capable of transformation), wherein said microorganism is a *Bacillus sp*; (ii) producing a DNA construct *in vitro*, wherein said DNA construct comprises an incoming sequence of interest, flanked on each side by a homology box, wherein said homology boxes are flanked by non-homologous sequences which are non-critical targets for said microorganism to initiate uptake of said DNA construct; and (iii) directly transforming said microorganism with said DNA construct such that the DNA construct becomes integrated into the chromosome of said microorganism.

Cooper et al., EP 0761815 A2, throughout the patent and abstract, teach methods of producing a transformed *Bacillus thuringiensis* by introducing a DNA construct *in vitro*, wherein said DNA construct comprises an incoming sequence of interest that comprise mutations within the homologous *spoVBt1* gene (Example 2, p. 14, lines 16-20 and Figure 8; for example, as in instant claim 6) that has been inserted into the Psb1219 plasmid, (as in instant claim 11), and flanked on each side by the lateral sequences of the homologous *spoVBt1* gene, (p. 5, lines 41-50) said lateral

spoVBt1 gene sequences reading on homology boxes, wherein said homology boxes are flanked by non-homologous sequences from the ancestral pBR322 plasmid that are, absent evidence to the contrary, "non-critical" targets for said microorganism to initiate uptake of said DNA construct; and (iii) directly transforming said microorganism with said DNA construct such that the DNA construct becomes integrated into endogenous *spoVBt1* site on the chromosome of said *B. subtilis*, (p. 15, line 24-p. 16, line 45). Cooper at p. 5, lines 41-50, teach spoV sequences homologous to the Bacillus chromosome "in the range of about 15-1600 nucleotide bases and more preferably 200-1200", thereby teaching increasing the amount of homology from about 15 nucleotide bases to more preferably 200-1200. Cooper et al., in Example 2: Chromosomal Integration, at p. 14, line 11-p. 16, line 45, teach integration using homologous spoV fragments that have different lengths (p. 14, line 19 and p. 15, lines 16-17), which read on increasing the amount of homology by increasing the length of the homologous sequence.

Because the methods taught by Cooper et al., EP 0761815 A2 disclose the steps of the instant claimed invention, and because Example 4 in the instant specification discloses that "[t]he non-homologous flanks were derived from the TOPO cloning vector and were of E. coli based plasmid origin; therefore, the sequences were not expected to have any significant homology to regions in the Bacillus chromosome", absent evidence to the contrary, the non-homologous sequences supplied by the vector, are "non-critical targets" that act to initiate uptake of the DNA construct, in the same way as the instant claimed invention.

Response to Arguments

Applicant argues that even though Cooper et al., EP 0761815 A2, discloses homologous regions (i.e., homology boxes), Cooper et al. does not disclose homologous regions (i.e., homology boxes) flanked by non-homologous regions, as recited in the amended claims.

Applicant's arguments filed 12/16/2004, have been fully considered but they are not persuasive. The patent of Cooper et al., EP 0761815 A2, teaches homologous regions that read on homology boxes flanking a *B. thuringiensis* mutated homologous *spoVBt1* gene, said homology boxes being flanked by non-homologous sequences of pBR322 plasmid (Example 2, p. 14, lines 16-20 and Figure 8).

New Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1, 4-7, 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Niaudet et al., Journal of Bacteriology, July 1985, Vol. 163, No. 1, pp.

111-120 (cited on PTO-892, mailed 10/20/2003) and Hahn et al., Molecular Microbiology (1996), vol. 21, no. 4, pp. 763-775 (cited on PTO-892, mailed 10/20/2003).

The claims are drawn to methods of transformation, wherein the Bacillus is a super-competent strain (as in claim 4) and is a Pxyl-comK strain (as in claim 5).

Niaudet et al., throughout the publication and abstract, and at p. 111, para 3, line 62-col. 4, line 16, col. 6, line 1-col. 9, line 22, teach methods of producing a transformed *Bacillus subtilis* (col. 2, lines 27-57) by introducing a DNA construct *in vitro*, wherein said DNA construct comprises an incoming sequence of interest that is a DNA fragment of a pHV32 plasmid (p. 113, caption to Fig. 1; for example, as in instant claim 7) which has been engineered into a pHV453 plasmid, (col. 5, lines 17-col. 34; and as in instant claim 11), and flanked on each side by the lateral sequences of the homologous sequences thyB and X (Niaudet at p. 113, para 2, and Fig. 1), which read on the homology boxes of the instant claims, wherein said homology boxes are flanked by non-homologous sequences of pHV453 plasmid that are, absent evidence to the contrary, "non-critical" targets for said microorganism to initiate uptake of said DNA construct; and (iii) directly transforming said microorganism with said DNA construct (p. 113, para 3-4) such that the DNA construct becomes integrated into the chromosome of said *B. subtilis*, (pp. 112-113, bridging paragraph and Figures 4 and 5). Niaudet, at p. 117, para 3-6, p. 119, para 4, and Fig. 5, teaches increasing the amount of sequence homology between a target sequence and a DNA construct, wherein **M** is a heterologous DNA segment and **a**, **b**, **c**, **k**, **l**, and **m** are homologous sequences flanking

M and wherein ω is added, resulting in an increase in the amount of sequence homology.

Because the methods taught by Niaudet disclose the steps of the instant claimed invention, and because Example 4 in the instant specification discloses that "[t]he non-homologous flanks were derived from the TOPO cloning vector and were of E. coli based plasmid origin; therefore, the sequences were not expected to have any significant homology to regions in the Bacillus chromosome", absent evidence to the contrary, the non-homologous sequences supplied by the pHV453 plasmid, are "non-critical targets" that act to initiate uptake of the DNA construct, in the same way as the instant claimed invention.

Niaudet et al., do not teach methods of producing a transformed microorganism, wherein said microorganism is a *Bacillus sp.*; and wherein the *Bacillus* is a super-competent strain (as in claim 4) and is a Pxyl-comK strain (as in claim 5).

Hahn et al., throughout the publication and abstract, teach methods of transformation involving *Bacillus subtilis* containing a PxylA-comK construct in order to place synthesis of ComK, which has been identified as the competence transcription factor, (p. 763, para 1), under the control of a xylose-regulated promoter (PxylA), (p. 764, para 3). Hahn et al., teach that:

> The data presented in this study suggest that ComK is sufficient as well as necessary for late-competence gene transcription. The induction of ComK synthesis in a PxylA-comk strain results in a high level of transformability, and suffices to activate the transcription of all the necessary late-competence genes, even in complex medium.

Hahn at p. 769, para 3.

It would have been prima facie obvious at the time the invention was made for one of ordinary skill in the art to have used methods of producing a transformed microorganism, comprising a sequence of interest flanked by homology boxes flanked by non-homology sequences, wherein said microorganism is a *Bacillus sp.*; and wherein the *Bacillus* is a super-competent strain (as in claim 4) and is a Pxyl-comK strain (as in claim 5).

One of ordinary skill in the art would have been motivated to have used *Bacillus* that is a super-competent strain and is a Pxyl-comK strain because Hahn et al. teach that the induction of ComK synthesis in a PxylA-comk strain results in a high level of transformability and is inducible by xylose.

One of ordinary skill in the art would have had a reasonable expectation of success, absent evidence to the contrary, because Hahn et al. teach transformation using a *Bacillus* that is a Pxyl-comK strain, and is a super-competent strain.

15. Claims 1, 4-7 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over van Sinderen and Venema, Journal of Bacteriology, Sept 1994, Vol. 176, No. 18, pp. 5762-5770 (cited on PTO-892, mailed 10/20/2003; formerly referred to a "Venema") and Hahn et al., Molecular Microbiology (1996), vol. 21, no. 4, pp. 763-775 (cited on PTO-892, mailed 10/20/2003).

The claims are drawn to methods of transformation, wherein the Bacillus is a super-competent strain (as in claim 4) and is a Pxyl-comK strain (as in claim 5).

van Sinderen and Venema, throughout the publication and abstract, teach methods of producing a transformed *Bacillus subtilis* (col. 2, lines 27-57) by introducing a DNA construct *in vitro*, wherein said DNA construct comprises an incoming sequence of interest that is a DNA fragment encoding a *spoVG-lacZ* fusion protein (p. 5764, caption to Fig. 1), wherein spoVG is homologous *Bacillus* DNA, (p. 5762, para 2), and lacZ is heterologous DNA, (p. 5763, para 4), that have been engineered into the pBTW312 plasmid, (col. 5, lines 17-col. 34; and as in instant claim 11), and flanked on each side by the lateral sequences of the homologous *B. subtilis amyE* sequences (van Sinderen and Venema at p. 5764, caption to Fig. 1), which read on the homology boxes of the instant claims, wherein said homology boxes are flanked by non-homologous sequences of the pBTW312 plasmid that are, absent evidence to the contrary, "non-critical" targets for said microorganism to initiate uptake of said DNA construct; and (iii) directly transforming said microorganism with said DNA construct (p. 5764, para 4) such that the DNA construct becomes integrated into the chromosome of said *B. subtilis*, (p. 5765, para 5-p. 5767, para 1.

Because the methods taught by van Sinderen and Venema disclose the steps of the instant claimed invention, and because Example 4 in the instant specification discloses that "[t]he non-homologous flanks were derived from the TOPO cloning vector and were of E. coli based plasmid origin; therefore, the sequences were not expected to have any significant homology to regions in the Bacillus chromosome", absent evidence to the contrary, the non-homologous sequences supplied by the vector, are "non-critical

targets" that act to initiate uptake of the DNA construct, in the same way as the instant claimed invention.

van Sinderen and Venema do not teach methods of producing a transformed microorganism, wherein said microorganism is a *Bacillus sp.*; and wherein the *Bacillus* is a super-competent strain (as in claim 4) and is a Pxyl-comK strain (as in claim 5).

Hahn et al., throughout the publication and abstract, teach methods of transformation involving *Bacillus subtilis* containing a PxylA-comK construct in order to place synthesis of ComK, which has been identified as the competence transcription factor, (p. 763, para 1), under the control of a xylose-regulated promoter (PxylA), (p. 764, para 3). Hahn et al., teach that:

> The data presented in this study suggest that ComK is sufficient as well as necessary for late-competence gene transcription. The induction of ComK synthesis in a PxylA-comk strain results in a high level of transformability, and suffices to activate the transcription of all the necessary late-competence genes, even in complex medium.

Hahn at p. 769, para 3.

It would have been prima facie obvious at the time the invention was made for one of ordinary skill in the art to have used methods of producing a transformed microorganism, comprising a sequence of interest flanked by homology boxes flanked by non-homology sequences, wherein said microorganism is a *Bacillus sp.*; and wherein the *Bacillus* is a super-competent strain (as in claim 4) and is a Pxyl-comK strain (as in claim 5).

One of ordinary skill in the art would have been motivated to have used *Bacillus* that is a super-competent strain and is a Pxyl-comK strain because Hahn et al. teach

that the induction of ComK synthesis in a PxylA-comk strain results in a high level of transformability and is inducible by xylose.

One of ordinary skill in the art would have had a reasonable expectation of success, absent evidence to the contrary, because Hahn et al. teach transformation using a *Bacillus* that is a Pxyl-comK strain, and is a super-competent strain.

16. Claims 1, 4-7 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fahnestock et al., US 4,828,994 (cited on PTO-892, mailed 10/20/2003) and Hahn et al., Molecular Microbiology (1996), vol. 21, no. 4, pp. 763-775 (cited on PTO-892, mailed 10/20/2003).

The claims are drawn to methods of transformation, wherein the Bacillus is a super-competent strain (as in claim 4) and is a Pxyl-comK strain (as in claim 5).

Fahnestock et al., US 4,828,994, throughout the patent and abstract, and at col. 3, line 62-col. 4, line 16, col. 6, line 1-col. 9, line 22, teach methods of producing a transformed *Bacillus subtilis* (col. 2, lines 27-57) by introducing a DNA construct *in vitro*, wherein said DNA construct comprises an incoming sequence of interest that is a DNA fragment of a heterologous functional cat gene (col. 4, lines 4-13; for example, as in instant claim 7) inserted into a cloned homologous apr gene (col. 5, lines 1-61; for example, as in instant claim 6) that has been inserted into a shuttle vector, (as in instant claim 10), which is capable of transformation and replication in both *E. coli* and *B. subtilis*, (col. 5, lines 17-col. 34); said apr gene coding for the *B. subtilis* protease subtilisin (col. 3, lines 5-8, fig. 1), and flanked on each side by the lateral sequences of

the homologous apr gene, said lateral apr sequences reading on homology boxes, wherein said homology boxes are flanked by non-homologous sequences from said vector that are, absent evidence to the contrary, "non-critical" targets for said microorganism to initiate uptake of said DNA construct; and (iii) directly transforming said microorganism with said DNA construct such that the DNA construct becomes integrated into endogenous apr gene on the chromosome of said *B. subtilis*, (col. 7, lines 31-54) in order to inactivate said endogenous apr gene (col. 2, line 58-col. 3, line 2; col. 3, lines 47-53).

Because the methods taught by Fahnestock disclose the steps of the instant claimed invention, and because Example 4 in the instant specification discloses that "[t]he non-homologous flanks were derived from the TOPO cloning vector and were of E. coli based plasmid origin; therefore, the sequences were not expected to have any significant homology to regions in the Bacillus chromosome", absent evidence to the contrary, the non-homologous sequences supplied by the vector, are "non-critical targets" that act to initiate uptake of the DNA construct, in the same way as the instant claimed invention.

Fahnestock et al., US 4,828,994, do not teach methods of producing a transformed microorganism, wherein said microorganism is a *Bacillus sp.*; and wherein the *Bacillus* is a super-competent strain (as in claim 4) and is a Pxyl-comK strain (as in claim 5).

Hahn et al., throughout the publication and abstract, teach methods of transformation involving *Bacillus subtilis* containing a PxylA-comK construct in order to

place synthesis of ComK, which has been identified as the competence transcription factor, (p. 763, para 1), under the control of a xylose-regulated promoter (PxylA), (p. 764, para 3). Hahn et al., teach that:

> The data presented in this study suggest that ComK is sufficient as well as necessary for late-competence gene transcription. The induction of ComK synthesis in a PxylA-comk strain results in a high level of transformability, and suffices to activate the transcription of all the necessary late-competence genes, even in complex medium.

Hahn at p. 769, para 3.

It would have been prima facie obvious at the time the invention was made for one of ordinary skill in the art to have used methods of producing a transformed microorganism, comprising a sequence of interest flanked by homology boxes flanked by non-homology sequences, wherein said microorganism is a *Bacillus sp.*; and wherein the *Bacillus* is a super-competent strain (as in claim 4) and is a Pxyl-comK strain (as in claim 5).

One of ordinary skill in the art would have been motivated to have used *Bacillus* that is a super-competent strain and is a Pxyl-comK strain because Hahn et al. teach that the induction of ComK synthesis in a PxylA-comk strain results in a high level of transformability and is inducible by xylose.

One of ordinary skill in the art would have had a reasonable expectation of success, absent evidence to the contrary, because Hahn et al. teach transformation using a *Bacillus* that is a Pxyl-comK strain, and is a super-competent strain.

17. Claims 1, 4-7, 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cooper et al., EP 0761815 A2 (cited on PTO-892, mailed 10/20/2003), and Hahn et al., Molecular Microbiology (1996), vol. 21, no. 4, pp. 763-775 (cited on PTO-892, mailed 10/20/2003).

The claims are drawn to methods of transformation, wherein the Bacillus is a super-competent strain (as in claim 4) and is a Pxyl-comK strain (as in claim 5).

Cooper et al., EP 0761815 A2, throughout the patent and abstract, teach methods of producing a transformed *Bacillus thuringiensis* by introducing a DNA construct *in vitro*, wherein said DNA construct comprises an incoming sequence of interest that comprise mutations within the homologous *spoVBt1* gene (Example 2, p. 14, lines 16-20 and Figure 8; for example, as in instant claim 6) that has been inserted into the Psb1219 plasmid, (as in instant claim 11), and flanked on each side by the lateral sequences of the homologous *spoVBt1* gene, (p. 5, lines 41-50) said lateral *spoVBt1* gene sequences reading on homology boxes, wherein said homology boxes are flanked by non-homologous sequences from the ancestral pBR322 plasmid that are, absent evidence to the contrary, "non-critical" targets for said microorganism to initiate uptake of said DNA construct; and (iii) directly transforming said microorganism with said DNA construct such that the DNA construct becomes integrated into endogenous *spoVBt1* site on the chromosome of said *B. subtilis*, (p. 15, line 24-p. 16, line 45). Cooper at p. 5, lines 41-50, teach spoV sequences homologous to the Bacillus chromosome "in the range of about 15-1600 nucleotide bases and more preferably 200-1200", thereby teaching increasing the amount of homology between the target and the

construct (as in claim 12), from about 15 nucleotide bases to more preferably 200-1200. Cooper et al., in Example 2: Chromosomal Integration, at p. 14, line 11-p. 16, line 45, teach integration using homologous spoV fragments that have different lengths (p. 14, line 19 and p. 15, lines 16-17), which read on increasing the amount of homology by increasing the length of the homologous sequence.

Because the methods taught by Cooper et al., EP 0761815 A2 disclose the steps of the instant claimed invention, and because Example 4 in the instant specification discloses that "[t]he non-homologous flanks were derived from the TOPO cloning vector and were of E. coli based plasmid origin; therefore, the sequences were not expected to have any significant homology to regions in the Bacillus chromosome", absent evidence to the contrary, the non-homologous sequences supplied by the vector, are "non-critical targets" that act to initiate uptake of the DNA construct, in the same way as the instant claimed invention.

Cooper et al., EP 0761815 A2 do not teach methods of producing a transformed microorganism, wherein said microorganism is a *Bacillus sp.*; and wherein the *Bacillus* is a super-competent strain (as in claim 4) and is a Pxyl-comK strain (as in claim 5).

Hahn et al., throughout the publication and abstract, teach methods of transformation involving *Bacillus subtilis* containing a PxylA-comK construct in order to place synthesis of ComK, which has been identified as the competence transcription factor, (p. 763, para 1), under the control of a xylose-regulated promoter (PxylA), (p. 764, para 3). Hahn et al., teach that:

> The data presented in this study suggest that ComK is sufficient as well as necessary for late-competence gene transcription. The induction of ComK

> synthesis in a PxylA-comk strain results in a high level of transformability, and suffices to activate the transcription of all the necessary late-competence genes, even in complex medium.

Hahn at p. 769, para 3.

It would have been prima facie obvious at the time the invention was made for one of ordinary skill in the art to have used methods of producing a transformed microorganism, comprising a sequence of interest flanked by homology boxes flanked by non-homology sequences, wherein said microorganism is a *Bacillus sp.*; and wherein the *Bacillus* is a super-competent strain (as in claim 4) and is a Pxyl-comK strain (as in claim 5).

One of ordinary skill in the art would have been motivated to have used *Bacillus* that is a super-competent strain and is a Pxyl-comK strain because Hahn et al. teach that the induction of ComK synthesis in a PxylA-comk strain results in a high level of transformability and is inducible by xylose.

One of ordinary skill in the art would have had a reasonable expectation of success, absent evidence to the contrary, because Hahn et al. teach transformation using a *Bacillus* that is a Pxyl-comK strain, and is a super-competent strain.

18. Claims 1, 4-7, 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over van Sinderen and Venema, Journal of Bacteriology, Sept 1994, Vol. 176, No. 18, pp. 5762-5770 (cited on PTO-892, mailed 10/20/2003; formerly referred to a "Venema") and Hahn et al., Molecular Microbiology (1996), vol. 21, no. 4, pp. 763-775

(cited on PTO-892, mailed 10/20/2003) as applied to claims 1, 4-7 and 11 above, and further in view of Nikawa et al., Nucleic Acids Res. 1998, Vol. 26, no. 3, pp. 860-861.

The claims are drawn to methods of transformation, and increasing the amount of homology between the target and the construct (as in claim 12).

Neither of van Sinderen and Venema or Hahn et al., teach methods of producing a transformed microorganism where the amount of homology between the target and the construct is increased, (as in claim 12).

Nikawa et al., throughout the publication and abstract, and at p. 860, para 1, teach increasing the length of homology regions because the transformation efficiency of constructs "having small homology regions at both ends is inferior to that with DNA having long homology regions. Furthermore, the sequence polymorphism in different strain backgrounds will hinder homologous recombination when small homology regions are used. Elongation of the homology regions flanking the marker gene would solve this problem and several advanced methods have been reported." Nikawa at p. 860, para 1.

It would have been prima facie obvious at the time the invention was made for one of ordinary skill in the art to have used methods of producing a transformed microorganism, where the amount of homology between the target and the construct was increased, (as in claim 12).

One of ordinary skill in the art would have been motivated to have used methods of producing a transformed microorganism, where the amount of homology between the

target and the construct was increased in order to increase transformation efficiency, as taught by Nikawa et al.

One of ordinary skill in the art would have had a reasonable expectation of success, absent evidence to the contrary, because Nikawa et al. teach that increasing transformation by increasing the length of sequence homology was well known in the art.

19. Claims 1, 4-7, 10 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fahnestock et al., US 4,828,994 (cited on PTO-892, mailed 10/20/2003) and Hahn et al., Molecular Microbiology (1996), vol. 21, no. 4, pp. 763-775 (cited on PTO-892, mailed 10/20/2003) as applied to claims 1, 4-7 and 10 above, and further in view of Nikawa et al, Nucleic Acids Res. 1998, Vol. 26, no. 3, pp. 860-861.

The claims are drawn to methods of transformation, and increasing the amount of homology between the target and the construct (as in claim 12).

Neither of Fahnestock et al., US 4,828,994 or Hahn et al., teach methods of producing a transformed microorganism where the amount of homology between the target and the construct is increased, (as in claim 12).

Nikawa et al., throughout the publication and abstract, and at p. 860, para 1, teach increasing the length of homology regions because the transformation efficiency of constructs "having small homology regions at both ends is inferior to that with DNA having long homology regions. Furthermore, the sequence polymorphism in different strain backgrounds will hinder homologous recombination when small homology regions are used. Elongation of the homology regions flanking the marker gene would solve

this problem and several advanced methods have been reported." Nikawa at p. 860, para 1.

It would have been prima facie obvious at the time the invention was made for one of ordinary skill in the art to have used methods of producing a transformed microorganism, where the amount of homology between the target and the construct was increased, (as in claim 12).

One of ordinary skill in the art would have been motivated to have used methods of producing a transformed microorganism, where the amount of homology between the target and the construct was increased in order to increase transformation efficiency as taught by Nikawa et al.

One of ordinary skill in the art would have had a reasonable expectation of success, absent evidence to the contrary, because Nikawa et al. teach that increasing transformation by increasing the length of sequence homology was well known in the art.

Conclusion

20. Claims 1, 4-7 and 10-12 are rejected.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Shibuya whose telephone number is (571) 272-0806. The examiner can normally be reached on M-F, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mark L. Shibuya
Examiner
Art Unit 1639

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